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ORIGINAL COMMUNICATION

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Parkinsonism with excessive daytime sleepiness

A narcolepsy-like disorder?

Abstract *Background* Parkinsonian patients with excessive daytime sleepiness (EDS), hallucinations, REM sleep behavior disorder (RBD), short mean sleep latencies, and sleep-onset REM periods (SOREMP) on multiple sleep latency tests (MSLT) have been reported. In these patients a narcolepsy-like pathophysiology of sleep-wake disturbances has been suggested. *Patients and methods* We studied 14 consecutive patients with Parkinsonism and EDS. Standard studies included assessment of duration and severity of Parkinsonism (Hoehn & Yahr score), Epworth sleepiness score (ESS), history of "REM-symptoms" (RBD/hallucinations/sleep paralysis/cataplexy-like episodes), polysomnography (PSG), MSLT, and measurement of cerebrospinal fluid (CSF) levels of hypocretin-1 (orexin A). *Results* There were 12 men and 2 women (mean age 69 years; range 54–82). The mean duration and the Hoehn&Yahr score were 6.3 years and 2.2, respectively. Diagnoses included idiopathic Parkinson's disease (IPD, n = 10), dementia with diffuse Lewy bodies (n = 3), and multisystem atrophy (n = 1). The ESS was ≥10 in all patients (mean 12; range 10–18). "REM-symptoms" were reported by all but two patients (hallucinations: n = 9; RBD: n = 9). None of the patients reported cataplexy-like symptoms or sleep paralysis. On PSG sleep apnea (apnea hypopnea index > 10/h, n = 7), periodic limb movements during sleep (PLMS-index > 10/h, n = 6), and features of RBD (n = 5) were found. On MSLT mean sleep latency was < 5 minutes in 10 patients, and SOREMP were found in two patients. When compared with controls (n = 20, mean 497 pg/ml; range 350–603), CSF hypocretin-1 levels were normal in 8 patients and low in 2 patients (221 and 307 pg/ml, respectively). *Conclusion* These findings do not support the hypothesis of a " final common pathway" in the pathophysiology of narcolepsy and Parkinsonism with EDS. Sleep apnea and PLMS may play a so-far underestimated role in the pathogenesis of EDS in Parkinsonian patients.

Key words Parkinsonism · narcolepsy · REM sleep behavior disorder · hypocretin · excessive daytime sleepiness · Epworth sleepiness score · sleep attacks

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Introduction

Several reports have documented the presence of excessive daytime sleepiness (EDS) with frequent napping and/or increased sleep time during daytime in a significant proportion (15–51 %) of patients with idiopathic Parkinson's disease (IPD) [1–6]. Self-reported EDS as estimated by an Epworth sleepiness score (ESS) > 10 has been found in up to 50 % of patients with IPD, with a frequency of falling asleep while driving in almost half of them [7]. It is noteworthy that sudden, irresistible, and overwhelming sleepiness that occurs without warning ("sleep attacks") in IPD may also occur in the absence of abnormal scores on the ESS. The sensitivity and specificity of an ESS > 10 for the occurrence of "sleep attacks" have been reported to be 71 % and 88 %, respectively [8].

Excessive daytime sleepiness has also been reported

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in other Parkinsonian disorders such as multisystem atrophy (MSA), dementia with Lewy bodies (DLB), and progressive supranuclear palsy (PSP) [9].

The etiology of EDS in Parkinsonian patients is probably multifactorial. Potential factors such as age, motor disability, disturbed nocturnal sleep (caused by sleep disordered breathing or periodic leg movements), levodopa, dopamine agonists have been shown to be associated with the severity of EDS in some but not all studies [3, 6, 9, 10].

Hallucinations and REM sleep behavior disorder (RBD) are also frequently reported, often in combination, in Parkinsonian disorders including DLB and IPD [11]. Systematic studies suggest the presence of hallucinations in 26–40 % of IPD patients and in up to 62 % of DLB patients [12–14]. In a recent series RBD was found by history in 17 % and by polysomnography in 33 % of IPD patients [15]. The percentage of DLB and MSA patients with RBD may be as high as 72–100 % [14, 16]. The coexistence of Parkinsonian disorders with EDS, hallucinations, RBD and ≥2 sleep onset REM periods (SOREMP) on MSLT has suggested that there is a narcolepsy-like pathophysiology in these patients [9, 17].

Considering the high sensitivity and specificity of low cerebrospinal fluid (CSF) hypocretin-1 levels for the diagnosis of narcolepsy [18, 19], these measurements are of particular interest in Parkinsonism. Until today, however, studies on CSF hypocretin-1 in Parkinsonism have been rare and contradictory with reports of normal [20, 21], low [22], and undetectable levels [23].

The aim of this study was to test by means of a multimodal approach the hypothesis of a common pathway in the pathophysiology of both Parkinsonism with EDS and narcolepsy.

Patients and methods

We studied 14 patients (2 women and 12 men; mean age = 69 years, range 54–82) with Parkinsonism and subjective EDS. Demographic and clinical characteristics of the patients are summarized in Table 1. Ten patients were recruited at the University Hospital of Zurich (Switzerland), and four in the University Hospital "San Raffaele" of Milan (Italy). Idiopathic Parkinson's disease and other Parkinsonian disorders were diagnosed according to international criteria [24, 25]. The severity of Parkinsonism was assessed by the Hoehn and Yahr Disability scale.

Assessment included a detailed history, a clinical examination, sleep recordings, and laboratory tests.

History

History was obtained by means of standard sleep questionnaires, including questions on subjective estimation of EDS (Epworth Sleepiness Score) [26], "sleep attacks" (defined as short, unintended sleep episodes) and such "REM symptoms" as sleep paralysis, hallucinations, REM-sleep behavior disorder, and cataplexy-like episodes. Diagnosis of RBD by history was made according to the International Classification of Sleep Disorders. Minimal diagnostic criteria include body or limb movements, associated with dream mentation and at least one of the following symptoms: (potentially) harmful sleep behaviors, dreams that have been reported to be acted out, and sleep discontinuation because of sleep behavior [27]. A detailed history of current medication was also obtained.

Clinical examination

A completed neurological examination including a Mini Mental State Examination [28] was performed in all patients.

Sleep recordings

Polysomnography (PSG) was recorded and scored according to international criteria [29]. Sleep latencies and presence of SOREMP (epochs of REM sleep occurring within 15 minutes after the first sleep epoch) were determined on multiple sleep latency tests (MSLT). A polysomnographic diagnosis of RBD was made in the presence of increased submental EMG tone during REM sleep, in association with complex motor behaviors such as gesturing, jerking, reaching, punching, sitting, kicking, laughing, talking and yelling [29].

Laboratory tests

Lumbar punctures were performed between 11 a. m. and 4 p. m. with the patient in a lying position. CSF was immediately frozen at –80° C. Hypocretin-1 levels in CSF were measured by radio-immunnoassay (RIA) in crude CSF as previously described [21]. The detection limit is 20 pg/ml and the intra-assay variability is 4 %. In previous publications we used published reference levels [19]. Because of the high inter-assay variability of the RIA kit, we decided for the purpose of this study to standardize CSF hypocretin-1 levels to own reference CSF samples, and to compare values with those of a healthy control group (n = 20, mean age 44 years, range 17–79). Based on our control group data, we consider CSF hypocretin-1 levels < 320 pg/ml as abnormally low. The HLA haplotype DQB1*0602 was determined in five patients.

All patients gave written informed consent to participate in the study. The hypocretin-1 results of three patients have been reported before [30].

Results

The main results of the study are summarized in Table 1.

Patients

Diagnoses included idiopathic PD (PD, n = 10), dementia with Lewy bodies (DLB, n = 3), and multisystem atrophy (MSA, n = 1). Mean disease duration was 6.3 years (range 1–16), mean Hoehn&Yahr score 2.2 (range 1–3). All patients were taking antiparkinsonian drugs (levodopa, n = 8; pergolide, n = 3; cabergoline, n = 3; ropinirole, n = 1; pramipexole, n = 1), and two patients had cholinesterase inhibitors. One patient was additionally treated with clonazepam. All drugs had been taken at stable doses for at least 1 month before the beginning of the study.

Table 1

	Pat. 1 (RM)	Pat. 2 (EL)	Pat. 3 (KF)	Pat. 4 (VO)	Pat. 5 (RP)	Pat. 6 (PM)	Pat. 7 (SP)	Pat. 8 (HH)	Pat. 9 (FT)	Pat. 10 (GS)	Pat. 11 (SL)	Pat. 12 (IM)	Pat. 13 (HG)	Pat. 14 (RM)
Age	60	74	82	65	70	65	59	65	78	73	74	77	71	54
Gender	male	male	male	male	female	male	male	male	male	male	male	female	male	male
Center	Zurich	Zurich	Zurich	Zurich	Zurich	Zurich	Zurich	Zurich	Milano	Milano	Milano	Milano	Zurich	Zurich
Parkinsonian symptoms														
Diagnosis	DLB	DLB	DLB	MSA	IPD	IPD	IPD	IPD	IPD	IPD	IPD	IPD	IPD	IPD
Disease duration (years)	3	3	4	16	3	15	8	6	1	3	15	1	3	7
Hoehn and Yahr Score	2	3	NA	3	1	2	2	2	2	2	3	1	2	3
Mini Mental Score	23	20	25	19	23	28	30	30	24	22	24	25	NA	29
Treatment	Levodopa 750 mg/d	CI 5 mg/d Clonazepam	CI 10 mg/d	Levodopa 750 mg/d Cabergoline 6 mg/d	Cabergoline 3 mg/d	Levodopa 500 mg/d Ropirinol 15 mg/d	Levodopa 1125 mg/d Pergolide 3 mg/d	Pergolide 4 mg/d	Levodopa 200 mg/d	Levodopa 300 mg/d	Levodopa 800 mg/d	Pergolide 1 mg/d	Cabergoline 2 mg/d	Levodopa 1700 mg/d Pramipexol 1 mg/d
Sleep-wake symptoms														
Excessive daytime sleepiness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epworth Sleepiness Score	14	12	11	12	15	18	11	12	11	10	13	10	10	11
"Sleep attacks"	+	–	–	–	–	–	–	–	–	–	+	–	+	–
Hallucinations	+	+	+	+	+	+	+	–	+	–	+	–	–	–
Sleep paralysis	–	–	–	–	–	–	–	–	–	–	–	–	–	–
REM sleep behavior disorder*	+	+	+	+	–	+	–	–	+	+	–	+	–	+
Cataplexy/ unintended falls	–/–	–/+	–/+	–/+	–/–	–/+	–/–	–/+	–/+	–/–	–/–	–/–	–/–	–/–
Actigraphy														
% of time "asleep"	NA	NA	NA	NA	43 %	36 %	39 %	40 %	NA	NA	NA	NA	42 %	NA
Polysomnography														
Sleep latency (min)	3	15	19	14	11	10	2	4	189	54	9	29	2	15
% NREM 3–4**	8	4	4	5	39	11	30	9	28	23	25	28	6	7
% REM sleep**	6	4	15	19	0	14	0	8	24	20	24	15	2	10
Apnea-Hypopnea-Index	10	9	17	24	7	8	24	10	12	10	8	11	58	13
PLM-Index	< 5	13	< 5	< 5	< 5	< 5	< 5	15	32	27	38	30	< 5	< 5
REM sleep behavior disorder	–	+	–	–	–	–	–	–	+	+	–	+	–	+
Multiple sleep latency test														
Mean sleep latency (min)	1.3	1.3	2.5	NA	2.4	NA	1.1	4.3	3.8	9.3	4.3	7.1	1.6	2.6
# of SOREM/# of naps	0/4	0/4	0/4	NA	0/4	NA	0/4	0/4	1/5	0/5	0/5	0/5	0/4	4/4
DQB1*0602	+	NA	NA	+	NA	NA	NA	NA	–	NA	–	–	NA	NA
Hypocretin-1 (pg/mL)	608	432	615	221	591	NA	NA	NA	380	307	654	537	NA	454

DLB dementia with Lewy bodies; *MSA* multisystem atrophy; *IPD* idiopathic Parkinson's disease; *CI* cholinesterase inhibitor; *PLM* periodic limb movements in sleep; *SOREM* sleep onset REM periods; *NA* not available
* by history; ** expressed as % of total sleep time

History

All patients had an Epworth sleepiness score ≥10 (mean 12, range 10–18). "Sleep attacks" were reported by three patients. Hallucinations were reported by five patients with idiopathic PD, three patients with DLB, and one patient with MSA. None of the patients reported sleep paralysis. Six patients (2 DLB, 4 PD) reported recurrent falls, but in none were the falls triggered by emotions (cataplexy-like episodes). In nine patients, history (obtained by the patients or their caregivers/relatives) fulfilled the clinical criteria for RBD.

Sleep recordings

On polysomnography the mean sleep latency (SL) was 27 minutes (range 2–189), slow-wave-sleep (SWS) represented 16% of total sleep time (mean, range: 4–39%) and REM sleep represented 12% of total sleep time (mean, range: 0–24%) of total sleep time. Two patients had no REM sleep during polysomnography. REM sleep behavior disorder was diagnosed polysomnographically in five patients. Periodic limb movements in sleep (PLMS >10) were documented in six patients with a PLMS-Index ranging from 13/h to 38/h. An abnormal apnea-hypopnea-index (AHI >10) was found in seven patients with an AHI ranging from 11/h to 58/h.

On MSLT the mean sleep latency was 3.5 min (range: 1.1–9.3 min), with a mean sleep latency < 5 minutes in 10 out of 12 patients. Sleep onset REM periods (SOREMP) were found in patient 9 (in 1 out of 5 naps) and in patient 14 (in 4 out of 4 naps) (Fig. 1). In a few patients episodes of atonia and/or rudimentary rapid eye movements were observed during NREM sleep (Fig. 2). In five patients in whom the information was available, sleep was perceived subjectively in 18 of 20 naps.

The mean percentage of time "asleep" during actigraphy was 40% (range: 36–43%), corresponding to 9.6 hours (range 8.6–10.3) per day.

Laboratory tests

CSF hypocretin-1 ranged in our controls from 350 to 603 pg/ml (mean 497 pg/ml). Hypocretin-1 levels in CSF were detectable in all 10 patients tested. The mean hypocretin-1 level was 480 pg/ml (range 221–654 pg/ml). Patient 4 (221 pg/ml, MSA, disease duration 16 years), and patient 10 (307 pg/ml, IPD, disease duration 3 years) had lower levels than our control group. HLA DQB1*0602 was positive in two of the five patients tested.

Discussion

The aim of this study was to test the hypothesis of a narcolepsy-like pathophysiology in Parkinsonian patients with EDS. To our best knowledge, this is the first study in which a systematic and prospective multimodal approach including clinical assessment, specific sleep-wake questionnaires, neurophysiology and CSF hypocretin-1 measurements has been performed in patients with Parkinsonism and EDS.

The main results can be summarized as follows:

First, cataplexy-like symptoms and sleep paralysis were not found in our patients, not even in those report-

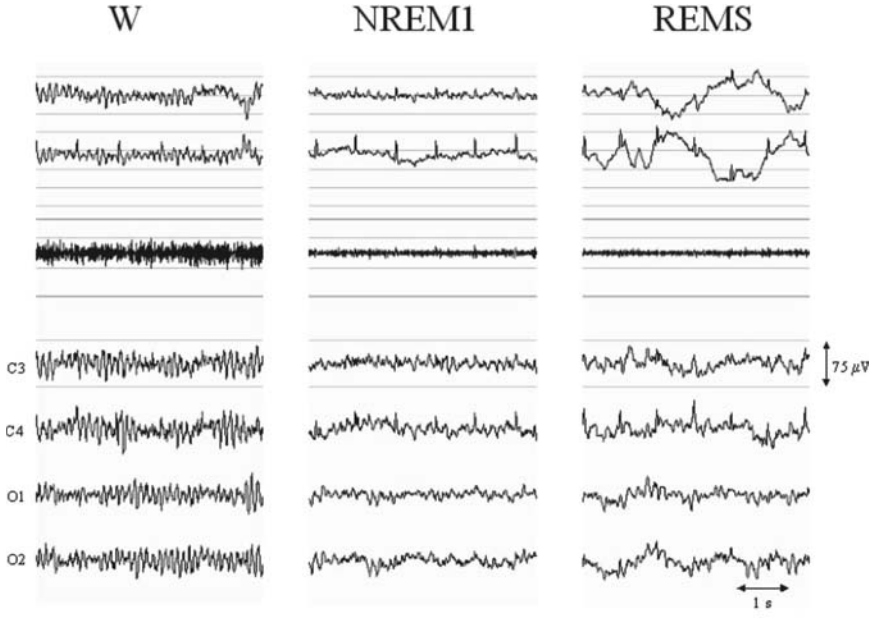

Fig. 1 54-year-old male patient (RM) with a 7-year history of idiopathic Parkinson's disease and with a subjective complaint of excessive daytime sleepiness. Epworth sleepiness score: 11/24. No episodes of sudden falling asleep while driving, cataplexy-like episodes, sleep paralysis, or hallucinations. History of violent, enacted dreams. Polysomnography: mild sleep-disordered breathing (apnea-hypopnea index = 13/hour) and loss of physiological atonia in REM sleep (Figure). No periodic limb movements in sleep (PLMS). Multiple sleep latency test: mean sleep latency of 2.6 minutes, SOREMP in 4 out of 4 naps

ing recurrent falls and RBD, in whom an underlying, common involvement of the pedunculo-pontine nucleus has been postulated [31, 32]. This finding is in accord with previous reports, in which cataplexy and sleep paralysis have not been found in PD with EDS and with or without hallucinations/RBD [11, 20, 33].

Second, sleep onset REM periods (SOREMP) were observed only in two of our 14 patients (14 %) and in 5 (10 %) out of 52 nap opportunities, respectively. Similarly, Rye et al. found SOREMP in only 10 % of 134 nap opportunities in IPD patients [1]. Other authors have reported higher frequencies of 29 % (≥ 1 SOREMP during MSLT on two consecutive days) and 39 % (≥ 1 SOREMP during a single MSLT) [4, 9]. The reason for these differences is unclear. Although SOREMP have been reported to be more frequent in patients with severe EDS [1, 4], the mean sleep latency found on MSLT in our patients was not longer than those of previous studies. Differences in duration/severity of PD, frequency of comorbidities, and medication could, however, play a role [32]. Furthermore, four of our patients (one of whom had SOREMP) had a Parkinsonian disorder other than IPD, conditions in which the frequency of SOREMP may be lower than in IPD [34]. Finally, identification of REM sleep in patients with Parkinsonian disorder is known to be difficult [35] and differs between sleep centers. We observed in a few patients dissociated states with atonia and/or rudimentary eye movements during NREM sleep 2 that did not fulfill the conventional scoring criteria for REM sleep (Fig. 2).

Third, hypocretin-1 levels in the cerebrospinal fluid were normal in 8 patients and low (but still > 200 pg/ml) in two patients. There was no evident association between hypocretin-1 levels and such features as RBD, hallucinations, Epworth Sleepiness score, and mean sleep latency on MSLT. It is noteworthy that the hypocretin-1 level was normal also in a single patient with a 7-year history of IPD, EDS, very short mean sleep latency on MSLT, and SOREMP in all four naps (Fig. 1). In two other reports of seven and four patients, respectively [20, 21], hypocretin-1 levels in IPD patients were also reported to be within the normal range. In a study reported in abstract form, Japanese authors also found normal levels in 16 of 19 Parkinsonian patients, and low but still detectable levels in the remaining three patients [22]. Conversely, Drouot and colleagues found significantly lower CSF hypocretin-1 levels in 19 IPD patients when compared with five controls (57 ± 14 vs 199 ± 34 pg/ml). CSF hypocretin-1 was undetectable in nine of these 19 patients [21]. Although detailed clinical and neurophysiological assessments are not available in these patients, differences in clinical characteristics may not be sufficient to explain the discrepancy of results. In fact, patients with long disease duration and advanced severity were included in our study as well, and the mean Epworth sleepiness score was similar in both series (12 and 11, respectively). In the French study, hypocretin-1 determinations were performed in ventricular CSF, which was obtained in the course of operative implantation of a deep brain stimulator. This different approach may explain their results.

Fourth, subjective EDS was confirmed by MSLT in most cases, with a mean sleep latency on MSLT < 5 min in ten of 12 patients. Mean latencies < 5 minutes have been found before in 40–50 % of IPD patients with EDS, in whom however inclusion criteria differed from those used in this study [4, 9]. It is noteworthy that awareness of sleep during naps was usually present in our patients, in whom sleepiness was also associated with abnormal Epworth sleepiness scores. Conversely, in Parkinsonian patients with objective but without subjective EDS (as assessed by Epworth sleepiness score), nap perception

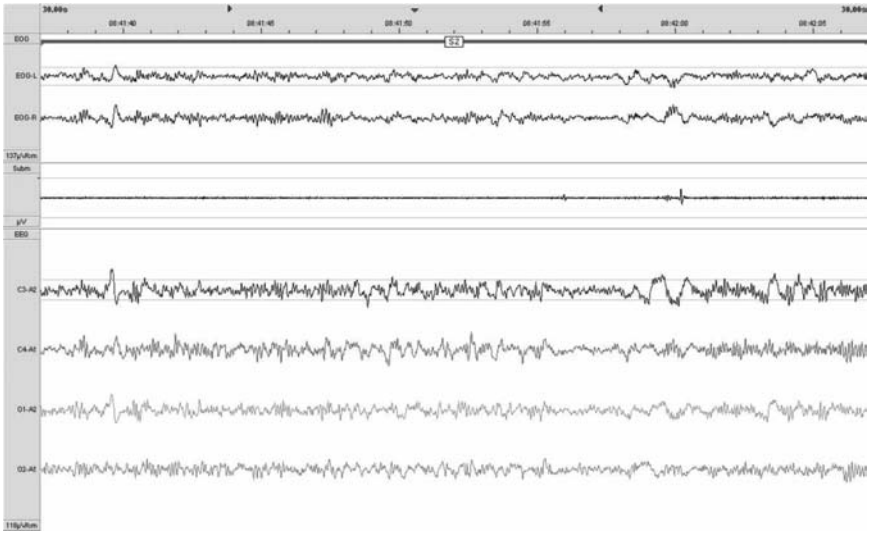

Fig. 2 71-year old male patient (HG) with a 3-year history of idiopathic Parkinson's disease and with a subjective complaint of excessive daytime sleepiness. Epworth sleepiness score: 10/24. One episode of sudden falling asleep ("sleep attack") while driving led to a severe car accident. No history of violent, enacted dreams, cataplexy-like episodes, sleep paralysis or hallucinations. Polysomnography: severe sleep-disordered breathing (apnea-hypopnea index = 58/hour, mainly mixed and central events, 16 % of time oxygen saturation < 90 %). No signs of REM sleep behavior disorder or periodic limb movements in sleep. Multiple sleep latency test: mean sleep latency of 1.6 minutes. In the absence of "clear-cut" sleep-onset REM episodes, a few episodes of muscle atonia with rudimentary eye movements are observed during NREM sleep 2 (Figure). With CPAP-treatment (7 cm H_2O) normalization of breathing during sleep. Discontinuation of CPAP after a few weeks because of mask claustrophobia

may be more impaired [34]. Our study also confirms that severe subjective and objective EDS can be a feature of Parkinsonism at early stages [9]. Two of our patients had a disease duration of one year. Similarly, Rye et al. reported an 18-year-old unmedicated IPD patient with a disease duration of two years in whom EDS was accompanied by a mean sleep latency on MSLT of 4.6 min (with SOREMP in one of five naps) [33]. Based on our observations, we suggest a contribution not only of dopaminergic drugs [4, 10, 36–38], but also of sleep disordered breathing and periodic limb movements in sleep to EDS in Parkinsonian disorders. Similarly, in a larger study of 54 IPD patients, Arnulf et al. reported an AHI > 15 in 20 %, and a PLMS-index > 15 in 15 % of her patients [9]. More recently, in a questionnaire survey a history of heavy snoring was found to correlate with self-reported EDS in patients with IPD [3]. Treatment of sleep-disordered breathing and PLMS in Parkinsonian patients with EDS may be warranted before stimulants are tried.

The main limitations of the study are the small sample size and the inclusion of patients with three different forms of Parkinson's syndrome.

In conclusion, our clinical, neurophysiological and CSF data do not support the hypothesis of a "final common pathway" in the pathophysiology of narcolepsy and Parkinsonism with EDS, not even when associated with hallucinations and REM sleep behavior. Sleep apnea and PLMS may play a so-far underestimated role in the pathogenesis of EDS in Parkinsonian disorders.

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